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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/463,890 | 04/28/2000 | ULRICH H. KOSZINOWSKI | 203676 | 6925 |
| 23460 | 7590 | 02/19/2010 | EXAMINER | |
| LEYDIG VOIT & MAYER, LTD | | | SAJJADI, FEREYDOUN GHOTB | |
| TWO PRUDENTIAL PLAZA, SUITE 4900 | | | ART UNIT | PAPER NUMBER |
| 180 NORTH STETSON AVENUE | | | | |
| CHICAGO, IL 60601-6731 | | | 1633 | |
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| | | | NOTIFICATION DATE | DELIVERY MODE |
| | | | 02/19/2010 | ELECTRONIC |

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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| | | | |
|------------------------------|------------------------|---------------------|--|
| Office Action Summary | Application No. | Applicant(s) | |
| | 09/463,890 | KOSZINOWSKI ET AL. | |
| | Examiner | Art Unit | |
| | FEREYDOUN G. SAJJADI | 1633 | |

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
 - If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
 - Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) Responsive to communication(s) filed on 12/7/2009.
- 2a) This action is **FINAL**. 2b) This action is non-final.
- 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) Claim(s) 36,37 and 40-70 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) Claim(s) _____ is/are allowed.
- 6) Claim(s) 36,37 and 40-70 is/are rejected.
- 7) Claim(s) _____ is/are objected to.
- 8) Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) The specification is objected to by the Examiner.
- 10) The drawing(s) filed on _____ is/are: a) accepted or b) objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) All b) Some * c) None of:
1. Certified copies of the priority documents have been received.
 2. Certified copies of the priority documents have been received in Application No. _____.
 3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ . |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date <u>12/7/2009</u> . | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| | 6) <input type="checkbox"/> Other: _____. |

DETAILED ACTION

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Request for Continued Examination

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicants' submission filed on December 7, 2009 that includes a response to the previous Office action dated August 6, 2009, has been entered. No claims have been amended, cancelled or newly added. Accordingly, claims 36, 37 and 40-70 remain pending in the application and are under current examination.

Information Disclosure Statement

The information disclosure statement (IDS) submitted on December 7, 2009 is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement has been considered by the examiner, and indicated as such on Applicants' IDS form.

Withdrawn Claim Rejections - 35 USC § 103

Claims 36, 37, 40-42, 45, 51, 57-60, and 63-66 were rejected under 35 U.S.C. 103(a) as being unpatentable over Messerle et al. (of record), in view of Chartier et al. (J. Virol. 70:4805-4810; 1996); claims 43 and 44 were rejected under 35 U.S.C. 103(a) as being unpatentable over Messerle et al., in view of Chartier et al. (J. Virol. 70:4805-4810; 1996), as applied to claims 36, 37, 40-42, 45, 51, 57-60, and 63-66 above, and further in view of Ehtisham et al. (1993) J. Virol. 67:5247-5252; claims 45-50 and 52-56 were rejected under 35 U.S.C. 103(a) as being unpatentable over Messerle et al. in view of Chartier et al. (J. Virol. 70:4805-4810; 1996), as applied to claims 36, 37, 40-42, 45, 51, 57-60, and 63-66 above, and further in view of Gage et al. (1992) J. Virol. 66:5509-5515; claims 60-62 were rejected under 35 U.S.C. 103(a) as being unpatentable over Messerle et al. in view of Chartier et al. (J. Virol. 70:4805-4810; 1996), as

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applied to claims 36, 37, 40-42, 45, 51, 57-60, and 63-66 above, and further in view Chen et al. (1987) Mol. Cell. Biol. 7:2745-2752; and claims 67-70 were rejected under 35 U.S.C. 103(a) as being unpatentable over Messerle et al., in view of Chartier et al. (J. Virol. 70:4805-4810; 1996), as applied to claims 36, 37, 40-42, 45, 51, 57-60, and 63-66 above, and further in view of Luckow et al. (1993) J. Virol. 67:4566-4579, in the previous Office action dated August 6, 2009.

Applicants' arguments supported by the evidence provided in the Rule 1.132 Declaration by co-inventor Ulrich H. Koszinowski, demonstrating that homologous recombination of herpesvirus genomes larger than 100 kb could not be successfully achieved in *E. coli* at the time of the instant invention, are found persuasive. Accordingly, the rejections under 35 USC § 103 are hereby withdrawn. Applicants' additional arguments are rendered moot in view of the withdrawn arguments. The claims are however subject to new rejections over the prior art as set forth below.

New Claim Rejections - 35 USC § 103

Claims 36, 37, 40-42, 45, 51, 57-60, and 63-66 are newly rejected under 35 U.S.C. 103(a) as being unpatentable over Messerle et al. (of record), in view of Kemble et al. (J. Virol. 70:2044-2048; 1996).

Messerle et al describe reconstituting two BAC/MCMV hybrid fragments wherein the hybrid vectors comprise BAC sequences and an infectious viral genomic sequence of >200kb (i.e. 235 kb minus ~15 kb), and further disclose that the constructs were used to produce MCMV virions (i.e., due to complementation between the two vectors upon co-transformation in eukaryotic host cells). The ability of the BAC vectors to produce infectious virus evidences that each of the vectors comprise “parts of the genome of a virus that are indispensable for replication and packaging”. Furthermore, Messerle et al. describe production of the BAC vectors by cotransfection in *E. coli* cells. Messerle et al. state that the purpose of constructing the BAC vectors was to facilitate the exchange of nonessential viral genes by any gene of choice without the need for further selection. Moreover, Messerle et al. notes that human CMV as well as mouse CMV comprises a region that is probably not essential for replication *in vitro* and clearly views human CMV as a potential vector.

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While Messerle et al. describe their BAC vectors as comprising two fragments, the generation of large full-length viral vectors by homologous recombination in eukaryotic cells was known in the prior art.

Kemble et al. describe the generation of human cytomegalovirus by cotransfected overlapping cosmid clones spanning the 230-kb genome into HF cells to regenerate infectious virus (Title, Abstract and first column, p. 2045). Thus providing the motivation to apply the methodology to generate full-length infectious herpesvirus.

The teachings of Messerle et al. and Kemble et al. are both directed to the reconstitution and generation of infectious herpesvirus. Therefore, it would have been *prima facie* obvious for a person of ordinary skill in the art, to combine their respective teachings and to use homologous recombination in eukaryotic cells using overlapping CMV sequences, to generate infectious HSV in a host cell, as instantly claimed, with a reasonable expectation of success, at the time of the instant invention. A person of ordinary skill in the art would have been motivated to generate a sequence contiguous HSV BAC vector, because such would obviate the need to manipulate two separate BAC fragments.

Claims 43 and 44 are newly rejected under 35 U.S.C. 103(a) as being unpatentable over Messerle et al., in view of Kemble et al. (J. Virol. 70:2044-2048; 1996), as applied to claims 36, 37, 40-42, 45, 51, 57-60, and 63-66 above, and further in view of Ehtisham et al. (1993) J. Virol. 67:5247-5252.

Messerle et al. describe reconstituting two BAC/MCMV hybrid fragments wherein the hybrid vectors comprise BAC sequences and an infectious viral genomic sequence of >200kb (i.e. 235 kb minus ~15 kb), and further disclose that the constructs were used to produce MCMV virions.

Kemble et al. describe the generation of human cytomegalovirus by cotransfected overlapping cosmid clones spanning the 230-kb genome into HF cells to regenerate infectious virus (Title, Abstract and first column, p. 2045).

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While Messerle et al. and Kemble et al. do not describe their viruses as including gamma herpes virus MHV68, such was known in the prior art. The method of Kemble et al. is further applicable to any large virus genome.

Ehtisham et al. describe murine herpes virus 68 (MHV-68) as a naturally occurring murine herpes virus closely related to the EBV of primates. (See especially the first paragraph after the abstract).

Therefore, it would have been *prima facie* obvious for a person of ordinary skill in the art, to apply homologous recombination mediated by eukaryotic cells, to generate infectious MHV-68 in a host cell, as instantly claimed, with a reasonable expectation of success, at the time of the instant invention. A person of ordinary skill in the art would have been motivated to generate a sequence contiguous MHV-68 BAC vector, because such would obviate the need to manipulate two or more separate BAC fragments.

Claims 45-50 and 52-56 are newly rejected under 35 U.S.C. 103(a) as being unpatentable over Messerle et al. in view of Kemble et al. (J. Virol. 70:2044-2048; 1996), as applied to claims 36, 37, 40-42, 45, 51, 57-60, and 63-66 above, and further in view of Gage et al. (1992) J. Virol. 66:5509-5515.

Messerle et al. describe reconstituting two BAC/MCMV hybrid fragments wherein the hybrid vectors comprise BAC sequences and an infectious viral genomic sequence of >200kb (i.e. 235 kb minus ~15 kb), and further disclose that the constructs were used to produce MCMV virions.

Kemble et al. describe the generation of human cytomegalovirus by cotransfected overlapping cosmid clones spanning the 230-kb genome into HF cells to regenerate infectious virus (Title, Abstract and first column, p. 2045).

While Messerle et al. and Kemble et al. describe recombination involving loxP sites, such was known in the prior art.

Gage et al. describe a method of inserting plasmid DNA into a herpes virus genome by Cre-lox recombination wherein the bacterial sequences are flanked by loxP sites (see especially the paragraph bridging pages 5509-5510, Figure 1 and the caption thereto) and further state the

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method has many advantages over methods of inserting bacterial DNA by homologous recombination using marker transfer (see especially the first full paragraph on page 5514).

Therefore, it would have been *prima facie* obvious for a person of ordinary skill in the art, at the time the invention was made to modify the method of producing a BAC comprising an infectious herpes virus genomic sequence according to the method of Gage et al. such that the product BAC comprises bacterial nucleic acid sequences flanked by loxP sites, with a reasonable expectation of success at the time of invention by Applicants. One would be motivated to use the method of Gage et al. in view of the many advantages of the method described in the teachings of Gage et al. because Gage et al. demonstrates the efficacy of the Cre-lox system for inserting bacterial DNA into the herpes virus genome.

Claims 60-62 are newly rejected under 35 U.S.C. 103(a) as being unpatentable over Messerle et al. in view of Kemble et al. (J. Virol. 70:2044-2048; 1996), as applied to claims 36, 37, 40-42, 45, 51, 57-60, and 63-66 above, and further in view Chen et al. (1987) Mol. Cell. Biol. 7:2745-2752.

Messerle et al. describe reconstituting two BAC/MCMV hybrid fragments wherein the hybrid vectors comprise BAC sequences and an infectious viral genomic sequence of >200kb (i.e. 235 kb minus ~15 kb), and further disclose that the constructs were used to produce MCMV virions.

Kemble et al. describe the generation of human cytomegalovirus by cotransfected overlapping cosmid clones spanning the 230-kb genome into HF cells to regenerate infectious virus (Title, Abstract and first column, p. 2045).

While Messerle et al. and Kemble et al. do not describe transfection of NIH3T3 fibroblasts, such was known in the prior art.

Chen et al. describe a method of efficiently transformation eukaryotic cells, including NIH3T3 cells, by a method involving calcium phosphate coprecipitation. (See especially the Abstract and Table 1)

Therefore, it would have been *prima facie* obvious for a person of ordinary skill in the art, at the time the invention was made to transfet NIH3T3 cells, with a reasonable expectation of success at the time of invention by Applicants. One would be motivated to use the NIH3T3

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cells, because Chen et al. state that the method provides efficient transformation for introducing DNA.

Claims 67-70 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Messerle et al., in view of Kemble et al. (J. Virol. 70:2044-2048; 1996), as applied to claims 36, 37, 40-42, 45, 51, 57-60, and 63-66 above, and further in view of Luckow et al. (1993) J. Virol. 67:4566-4579 (of record).

The claims are directed to a method of mutagenizing the infectious herpes virus genomic sequence of claim 36 comprising introducing the BAC of claim 36 into a bacterial host and exposing the BAC to mutagenizing DAN molecules, wherein there is a transposon in the mutagenizing DNA molecules.

Messerle et al. describe reconstituting two BAC/MCMV hybrid fragments wherein the hybrid vectors comprise BAC sequences and an infectious viral genomic sequence of >200kb (i.e. 235 kb minus ~15 kb), and further disclose that the constructs were used to produce MCMV virions. Messerle et al. state that the BACs will facilitate the exchange of nonessential viral genes by any gene of choice.

Kemble et al. describe the generation of human cytomegalovirus by cotransfected overlapping cosmid clones spanning the 230-kb genome into HF cells to regenerate infectious virus (Title, Abstract and first column, p. 2045).

While neither Messerle et al. nor Kemble et al. describe specifically mutagenizing the infectious HSV genomic sequence with a transposon, such was known in the prior art.

Luckow et al. describe the construction and use of BAC vectors that comprise an infectious viral genome sequence operatively fused to a mini-F replicon that allows autonomous replication and stable segregation of plasmids at low copy number in *E. coli*. The BAC vectors further comprise a selectable kanamycin resistance marker and attTn7 sites that allow transposon-mediated insertion of heterologous nucleic acid sequences into the vector (e.g. Abstract; page 4567, columns 1-2, bridging paragraph; Figure 1). Luckow et al further describe transposon-mediated mutagenesis at the attTn7 sites of different BAC vectors in *E. coli* to generate new vectors comprising a heterologous sequence encoding a desired polypeptide. (See

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especially the section entitled “Transposition of mini-Tn7 elements to target bacmids” bridging the left and right columns on page 4573).

Therefore, it would have been *prima facie* obvious for a person of ordinary skill in the art, at the time the invention was made to combine their respective teachings and use the transposon mediated DNA exchange described by Luckow et al. for the purpose of exchanging nonessential viral genes with gene of choice in the BACs of Messerle et al., with a reasonable expectation of success at the time of invention by Applicants. One would be motivated to combine the teachings of the prior art because Messerle et al. teaches that intended use of the BAC vectors described therein is to facilitate the exchange of nonessential CMV viral genes by any gene of choice and Luckow et al. teaches that the method of the transposon mediated DNA exchange described thereby provides many advantages over other methods of engineering viral genomic DNA comprised in BACs that were known in the prior art. (See especially the first full paragraph on page 4577.)

Conclusion

Claims 36, 37 and 40-70 are not allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to FEREYDOUN G. SAJJADI whose telephone number is (571)272-3311. The examiner can normally be reached on 6:30 AM-3:30 PM EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on (571) 272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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/Fereydoun G Sajjadi/
Primary Examiner, Art Unit 1633